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4 January 2005 via e-mail and First Class mail

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane (Room 1061)
Rockville, MD 20852

RE: Docket No. 2004D-0440, Guidance for Industry—Computerized Systems Used in Clinical Trails, September 2004, Revision 1

Dear Dockets Manager:

The Computer Validation Initiative Committee and Clinical Specialty Section, two Specialty Sections of the Society of Quality Assurance (SQA), have reviewed the referenced document and prepared the attached comments for consideration by the Food and Drug Administration.

The Society of Quality Assurance is a non-profit organization composed of quality assurance professionals responsible for interpreting, developing and executing quality programs according to a variety of regulations and directives worldwide. The subject comments, prepared and evaluated by these two Specialty Sections of SQA, are intended to provide additional perspective on the importance of controlling computerized systems before, during and after the conduct of a clinical study.

Sincerely,

Krista Kerr, Chair
Society of Quality Assurance Clinical Specialty Section

Patricia Miller (ATT)
Patricia Miller, Chair
Society of Quality Assurance Computer Validation Initiative Committee

Kevin Yount, RQAP-GLP, President
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General Comments

The Draft *Guidance for Industry: Computerized Systems Used in Clinical Trials* (hereafter, the Guidance) contains nine fundamental principles and comments on enforcement discretion while the agency is re-examining Part 11. Important modifications in this revision include references to predicate rules; for example under 21 CFR Parts 312.62, 511.1(b)(7)(ii) and 812.140, the clinical investigator must retain records required to be maintained under part 312, § 511.1(b) and § 812. Further, records must be adequate and accurate with respect to INDs (§ 312.57 and § 312.62) and complete in the case of INADs (§ 511.1(b)(7)ii), and accurate, complete and current in the case of IDEs (§ 812.140(a) and § 812.140(b)).

SQA is pleased to see an explicit recognition that paper and electronic record and signature components can co-exist as a hybrid system as long a predicate rules are met. We support the provision of additional methods for tracking changes in electronic records and clarification with respect to time/date stamps.

Throughout the document, SQA recommends greater consistency in the use of phrases such as "we recommend that…" or "we suggest that … ." Without greater certainty ascribed to FDA's position, we are concerned that industry may fail to take all necessary actions to meet the elements of this guidance. In addition, we believe that there is a need to provide additional guidance on specific forms of electronic records used in clinical trials. We noted, for instance, that the electronic case report form and electronic patient diary were highlighted in the original version but they have been removed from this most recent revision.

Comments on specific sections of the Guidance are provided below.

Section II - Background

Line Numbers	**Draft Guidance and *Comments***
Footnote 4	FDA is allowing original documents to be replaced by certified copies provided the copies are identical and have been verified as such.
Comment:	*We support the decision to allow original documents to be replaced by certified copies provided the copies are identical and have been verified as such.*

60-62	Computerized medical devices, diagnostic laboratory instruments, and instruments in analytical laboratories that are used in clinical trials are not the subject of this guidance.
Comment:	*Could the Agency please clarify why computerized medical devices, diagnostics laboratory instruments, and instruments in analytical laboratories would be considered exempt from this guidance? Devices/instruments, such as hematology/chemistry analyzers, digitized ECGs or angiograms and software used to analyze them, and software used for bioanalysis could be generating data that supports clinical studies.*
65-67	The principles in this guidance may be applied where supporting data or source documents are created (1) in hardcopy and later entered into a computerized system (2) by direct entry by a human into a computerized system, and (3) automatically by a computerized system.
Comment:	*Theses principles are clear and concise.*
76-77	We recommend that each study protocol identify at which steps a computerized system will be used to create, modify, maintain, archive, retrieve, or transmit data
Comment:	*Is the FDA asking that the protocols indicate how the databases will be maintained not only during the study but also after the study has been completed and the data are used for statistical analyses and report generation?*

Section III - General Principles

Line Numbers	Draft Guidance and *Comments*
95-96	When original observations are entered directly into a computerized system, the electronic record is the source document.
Comment:	*It might be more clear if electronic source documents were defined as the electronic record contained on the computerized system's durable storage media, rather than stating that the observations entered directly into a computerized system are the source document. Technology now allows patient data to be captured initially using devices that record the data on "flash" or "temporary" media prior to transferring the data to traditional storage media. The flash or temporary media can be procedurally and technically secure, but usually have size or volume limitations and are usually designed to be written-over once the data have been transferred.*

105-107	Firms should determine and document the need for audit trails based on a risk assessment that takes into consideration circumstances surrounding system use, the likelihood that information might be compromised, and any system vulnerabilities.
Comment:	*For any computerized application there is a likelihood that information could be compromised, in particular when editing capabilities exist. Under what circumstances would an audit trail not be necessary? May we have examples?*
107-109	We recommend that audit trails or other security methods used to capture electronic record activities document who made the changes, when, and why changes were made to the electronic record.
Comment:	*There is no predicate rule requiring a reason for change in clinical documentation. Could the agency please provide additional insight as to why this is now being recommended.*

Section V - Standard Operating Procedures

Line Numbers	Draft Guidance and *Comments*
137-146	We recommend that standard operating procedures (SOPs) pertinent to the use of the computerized system be available on site. We recommend that SOPs be established for the following: • System Setup/Installation • Data Collection and Handling • System Maintenance • Data Backup, Recovery, and Contingency Plans • Security • Change Control Alternative Recording Methods (in the case of system unavailability)
Comment:	*It is unclear if "on site" as used here means the investigator sites or sites where the system originated (CRO or Sponsor). While instructions for system use should be available, it does not seem appropriate to expect system SOPs like these to be maintained at investigator sites. Please clarify the intended meaning of the term "on site."*
146	We recommend that SOPs be established for ....Alternative Recording Methods (in the case of system unavailability)
Comment:	*Is FDA referring to paper, microfilm, and microfiche, or are there other methods that the Agency has under consideration?*

Section VI - Data Entry

Line Numbers	Draft Guidance and *Comments*
185-187	Computer-generated, time-stamped audit trails or information related to the creation, modification, or deletion of electronic records may be useful to ensure compliance with the appropriate rule.
Comment:	*We support the provision of additional methods for tracking changes in electronic records. We agree that, in addition to computer-generated, time-stamped audit trails, other methods are useful. We agree that "it is important to keep track of all changes made to information in the electronic records that document activities related to the conduct of a clinical trial." On the other hand, simply stating that controls such as computer-generated audit trails "may be useful" does not provide clear direction to the regulated community as to when such tools would be appropriate for specific clinical trial activities. Could you please clarify under what circumstances computer generated, time-stamped audit trails would not be useful?*
189-191	In addition, clinical investigators must, upon request by FDA, at reasonable times, permit agency employees to have access to, and copy and verify any required records or reports made by the investigator.
196-198	To facilitate FDA's inspection of this information, we recommend that clinical investigators retain either the original or a certified copy of any documentation created to track electronic records activities.
Comment:	*In these sections, it is unclear what the Agency's expectations are for documentation at an investigator site, specifically when data are directly captured and are maintained elsewhere (at a CRO or Sponsor location). Is the expectation that a copy of those data be maintained by the site?*
228-229	Some examples of methods for tracking changes to electronic records include:...Procedural controls that preclude unauthorized personnel from creating, modifying, or deleting electronic records or the data contained therein.
Comment:	*We support the provision of additional methods for tracking changes in electronic records. We agree that, in addition to computer-generated, time stamped audit trails, other methods are useful such as signed and dated printed versions of electronic records that identify what, when and by whom changes are made; signed and dated printed standard electronic file formatted versions of electronic records; and procedural controls that preclude unauthorized personnel from creating, modifying, or deleting electronic records.*
231-245	Date/Time Stamps
Comment:	*We appreciate the additional clarification that FDA does not expect documentation of time changes that systems make automatically to adjust to daylight savings time conventions. We agree that it is important to have a clear understanding of the time zone reference used.*

Section VII - System Features

Line Numbers	Draft Guidance and *Comments*
258-259	We recommend against the use of features that automatically enter data into a field when the field is bypassed
Comment:	*Agreed, documentation by exception should not be allowed.*
263, and 268-273	FDA expects to be able to reconstruct a clinical study submitted to the agency… As explained in the Part 11 Scope and Application guidance, FDA does not intend to object to required records that are archived in electronic format; non-electronic media such as microfilm, microfiche, and paper; or to a standard electronic file format (such as PDF, XML, or SGML). Persons must still comply with all predicate rule requirements, and the records themselves and any copies of required records should preserve their original content and meaning.
Comment:	*We agree that a decision on record retention be based upon predicate rules and a justified risk assessment and a determination of records' value over time. We support the Agency's decision not to object to required records that are archived in electronic format; non-electronic media such as microfilm, microfiche, and paper; or to a standard electronic file format (such as PDF, XML, or SGML). SQA is pleased to see an explicit recognition that paper and electronic record and signature components can co-exist as a hybrid system as long as predicate rules are met and the content and meaning of the records are preserved.*
278-280	It is not necessary to reprocess data from a study that can be fully reconstructed from available documentation. Therefore, actual application software, operation systems, and software development tools involved in processing of data or records do not need to be retained.
Comment:	*We support the addition of text to clarify that it is not necessary to reprocess data from a study that can be fully reconstructed from available documentation. Furthermore, we support the conclusion that actual application software, operation systems, and software development tools involved in processing of data or records do not need to be retained.*

Section VIII - System Security

Line Numbers	Draft Guidance and *Comments*
291	SOPs should be developed and implemented for handling and storing the system to prevent unauthorized access.
Comment:	*What does "storing the system" mean, in the context of this sentence? Does this mean backing up the database and all associated software used to access the database? If so, this appears to be inconsistent with the intent of lines 278-280.*

Section IX - System Dependability

Line Numbers	Draft Guidance and *Comments*
350-351	If validation is required, FDA may ask to see the regulated company's documentation that demonstrates software validation.
Comment:	*Please clarify if the FDA would expect to see a full set of validation documents at the study site. Since validation deliverables are normally voluminous, we recommend that the regulated company provide each site where their computerized systems is installed or used, with documentation that states the necessary validation documentation can be viewed at the sponsor location.*

401-409	In the case of off-the-shelf software, we recommend that the following be available to the agency on request: • A written design specification that describes what the software is intended to do and how it is intended to do it. • A written test plan based on the design specification, including both structural and functional analysis; and • Test results and an evaluation of how these results demonstrate that the pre-determined design specification has been met.
Comment:	*These lines project a need for more information than was previously necessary for off-the-shelf (OTS) software. Is this the intention? Please see below for further description.* *Design Specifications:* *Is this referring to a specification describing how the software will be used by the purchasing company, or does the FDA intend for the vendor design specification documentation to be obtained and available to inspectors? For OTS system software (operating systems, database tools, SAS, EXCEL, etc.) the FDA has not previously required a vendor evaluation or sponsor storage of design specs. While the FDA expects a vendor evaluation of OTS application software that includes a review of system development documentation (including design specs), sponsors have not been expected to have those design specs available for review by an FDA Inspector.* *We would appreciate additional clarification as to the FDA's expectations for design documentation.* *Structural and Functional Analysis:* *For OTS system software, there has not previously been a requirement for either structural or functional testing. These tools are indirectly proven to operate correctly by testing the application software.* *For OTS application software, the requirement has long been to have a test plan that reflects functional (validation) testing. We believe that structural testing should be accomplished by the vendor and assessed as part of the vendor evaluation. The vendor evaluation would address the information reviewed and found to exist relative to structural testing. Having the structural testing documentation to show an FDA inspector has not previously been expected.*

Definitions

Line Numbers	**Draft Guidance and *Comments***
566-570	Software Validation: Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through the software can be consistently fulfilled. *Design level validation* is that portion of the software that takes place in parts of the software life cycle before is delivered to the end user.
Comment:	*Specifications developed by the vendor may be different from the clients' actual use of the computerized system. We recommend the following definition be considered: Software Validation is a process to produce objective evidence according to its pre-determined specifications and test plan.*